October 28, 2019

Prof Christiane Woopen
Chair
European Group on Ethics in Science and New Technologies

Dear Ms Woopen,

I would like to thank you and your team for hosting such an engaging roundtable on the Ethics of Gene-editing on 16 October 2019. I was both pleased and privileged to have the opportunity to listen to the interesting and challenging presentations and be part of the discussion.

I would like to raise a few points that occurred to me during the session and in the immediate period afterwards. I appreciate that you may already be well into the drafting of your report but I hope you might be able to take some or all of these into consideration.

Regulation
Although your enquiry is concerned with ethical issues, you are no doubt aware that your group's work will feed into a larger discussion of the regulation/deregulation of the products of genome editing in the EU.

Most of my observations below link back to regulation in some way and indeed, given that sound regulation is rooted in societal values and ethics, I hope you are planning to make some comment on the regulatory landscape in your own report.

There was not much time to explore this issue during the roundtable. When I posed the question in the final session, "What is the purpose of regulation?" it was in response to assertions by the biotechnology industry that regulation should encourage innovation.

The purpose of regulation is to protect individuals and/or the environment. Regulation is also, in part, an attempt to deal, at a societal level, with uncertainty.

Regulation grounds our big ideas in the real world of real people whose lives are affected by a given technology but who, because of in-built power disparities in society, have less say in the development, research, marketing and global spread of these products.

EU law is clear that genome editing is genetic engineering. Genetic engineering, like any 'disruptive' technology (e.g. driverless cars, artificial intelligence), is fraught with uncertainties and as such requires strong regulation.

This is one reason why EU regulation is structured around the Precautionary Principle, which is not only concerned with the probability of the risks, both known and unknown, but the severity of the consequences and their irreversibility. The Precautionary Principle provides an ethical framework for

dealing with uncertainty by saying if there is risk, even if the probability of negative impacts is or seems low, we should either not proceed or proceed with extreme caution.

Within the EU, there are currently calls to replace the Precautionary Principle with the so-called Innovation Principle, the purpose of which is to ease the journey of new technologies into marketplaces.

However, as the technology for genome editing advances so does the realisation that our knowledge of genome functioning is still very incomplete.

To take a few examples from animal genome editing: a recent Wall St Journal investigation reported unintended effects including enlarged tongues and extra vertebrae. Brazil's plans to breed hornless dairy cattle, gene-edited with TALENs were recently abandoned when a study by the US Food and Drug Administration revealed that one of the experimental animals contained a sequence of bacterial DNA including a gene conferring antibiotic resistance. In theory, this antibiotic resistance gene could be taken up by any of the billions of bacteria present in a cow's gut or body and from there be spread beyond the farm.

Other research this year has shown that edited mouse genomes can acquire bovine DNA or goat DNA. This was traced to the standard culture medium for mouse cells, which contains DNA from whichever animal species it may have been extracted from.

An interesting example also arose recently from the world of plant biotechnology. Although the practice is becoming less common, biotechnology companies often add antibiotic resistant genes in their modifications. This aids research by serving as a marker to differentiate genetically modified plant cells.

Most recently in America, where it is common to consume genetically engineered food products, researchers at Washington State University found that when people eat these foods, the incorporated genetic material moves through the digestive system and can be released into the environment, including into wastewater treatment plants. Water treatment does not destroy this DNA and these antibiotic-resistant genes are able to pass on their resistance to other bacteria. The researchers say that while the magnitude of the effect is unknown it is likely that "…this probably has contributed to the spread of antibiotic resistance in the environment."

Studies like these, which are appearing with ever-greater frequency, suggest our greatest need is for regulatory precaution.

Benefits

Although there has been much fanfare around the development of genome editing, there are very few products that have been shown to work as intended and, therefore, are suitable for the marketplace. This means that much of this discussion around risk, benefit and need remains in the realm of the theoretical and academic. Of all these theoretical discussions, that of benefits is the least well explored.

Early in the roundtable, I raised this question of the benefits. Much of the push for investment in this technology is focused on claimed (but not proven) benefits, as is much of the push to deregulate the technology.

In pharmaceutical research, we rightly expect that benefits should be proven and that proposed new products should be the subject of comparative research that demonstrates how they perform

against other viable alternatives. We should expect no less of the products of genome editing, whatever their intended use.

This especially true for those products which are intended to be released into the environment where they can interact with other organisms and into the food system where they may be consumed, likely unknowingly, by vast number of individuals.

Speed and limitlessness

As an organisation, Beyond GM has become concerned with the speed of development in the field of genome editing.

In the world of biotechnology, as elsewhere, there is a building narrative of "the need for speed" – the need to hurry up and develop new technologies to address a range of cultural, health, sustainability and environmental issues.

However, acquiescence to notions of speed and urgency preclude asking two important questions: How? and Why?

Questions such as "Why are we doing this?" and "How will it be used?" underpin the ethical framework of most industries and are especially important in the realm of technological advances. If we cannot ask – and answer – these questions we lose the ability to judge whether the work we are doing is ethical.

I have observed with interest that the designers of artificial intelligence systems seem more willing to engage with such questions, while the designers of living genome-edited products tend to shy away from them or dismiss them as irrelevant.

What we are creating with genome editing could outlast us and be passed on to future generations. Therefore, in considering their use, we must take into account our responsibility to the future. If we don't allow for the possibility of saying "no" to proposed technological advances, or allow ourselves to place rational limits on them, we lose the ability to shape our world as well as our accountability for the things we shape.

Our organisation is also concerned with the much publicised (though theoretical) 'no limits' narrative that lies behind the application of genome editing.

I am sure that by the end of the roundtable you may all have felt that, in taking on this subject, you had bitten off more than you could easily chew! However, looking at those three areas of use together, I believe, exposed a core fallacy of genome editing – namely that its applications are 'limitless'.

No technology is without limits or consequences and yet limitlessness is now a major selling point for genome editing – though during the roundtable it was interesting to observe that how hard this point was driven home depended on which area of use was being explored.

Thus, in newer areas of application such as human genome editing the scientists who presented were much more cautious in their claims, and much more willing to admit the gaps in their understanding. In contrast, those individuals who spoke about plant genome editing later in the day, I believe, travelled deeply into the territory of 'limitless' propaganda.

These related notions of speed and limitlessness put extraordinary pressure on regulatory authorities either to find ways to 'put the brakes on' or to follow the path of least resistance and acquiesce to calls for deregulation. Responsible regulation is a middle ground between these two extremes.

We would also argue that promoting 'limitlessness' is highly unethical, not just because it is misleading but because of the way it skews the research and regulatory agendas and creates the kind of 'Wild West' referred to during the day.

CRISPR, for example, is so easy to use that it has spawned a completely new industry of 'rogue' start-ups, biohackers and genome-editing hobbyists. As far back as 2005 tech magazine, *Wired* published an article, which noted "*The era of garage biology is upon us. Want to participate? Take a moment to buy yourself a lab on eBay*." There is now a Biohacking Facebook Group with thousands of members sharing tips and tricks. Netflix has just released a mini-series, Unnatural Selection, which is not entirely uncritical of biohacking and in some places even appears to suggest it is a 'cool' thing to do.

Without regulation these companies and individuals would not be accountable to law, they would not be subject to precautionary measures about environmental releases or human/animal experimentation, nor would there be any clear guidelines on responsibility if and when things go wrong.

Upcoming uses for genome editing

In addition to the three broad themes discussed at the roundtable, there are other proposed uses for genome editing which are fast coming onto the biotechnology 'event horizon'. A recent IUCN report, for example, suggests that genome editing, synthetic biology and gene-drives could be used to resurrect extinct species, rebuild soil fertility or improve health and resilience in at-risk species that are being, directly or indirectly, impacted by things like climate change and loss of habitat. What are the consequences of such uses? How might they intersect with other areas of the environment or with human welfare? What are the ethical questions involved in releasing such organisms into the wild?

It is a relatively short step from re-engineering wild animals to conserve them to re-engineering them for other purposes. Geese, badgers and bison, for example, are all implicated in infecting farm animals with various diseases. What are the potential consequences of genetically 'editing' these wild animals so they don't impact farm animals? Could a genome-edited wild animal unwittingly become a reservoir for zoonotic diseases for which we do not yet have the viable treatments? What happens to engineered soil microorganisms when released in the wild? How might they alter the soil structure and microbiome if, for example, genetically engineered organisms become the dominant species?

The recent release of gene-edited, gene drive mosquitoes in Brazil provides some early insights. These insects were supposed to breed with native mosquitoes and produce weak offspring that would die quickly without passing on their altered genome. However, the offspring have proved to be robust and are now breeding well beyond their original breeding grounds. Mosquitoes are vectors for all kinds of disease in humans and animals – and for diseases that can be transferred from animals to humans – so this is potentially concerning.

This and other uses for genome editing – for instance, in warfare as biological weapons – needs to be considered as part of the whole picture of proposed uses – the 'How?' question – and we would advise extreme caution in liberalising regulations for this reason.

Relative values
Finally, I was interested to observe that although we talked about the same basic science in each session there was a tremendous divide between the relative value placed on humans vs animals vs plants and the way that this was expressed in terms of precaution.

It revealed a highly anthropogenic hierarchy of life, where there appeared to be some concern and acknowledgement of an interaction between the human genome and our 'humanness' and between the animal genome and concepts of 'animalness' – but little to no acknowledgment that there may be a link between the plant genome and 'plantness' (i.e. the integrity of the plant organism). Without some acknowledgement of that possibility, there is a much greater tendency to take chances, and to deny or diminish discussions around risk and error. The interconnectedness of the plant kingdom with the human and animal kingdom would seem to make this an important consideration.

As part of our A Bigger Conversation initiative, Beyond GM recently conducted a 'world café' on The Boundaries of Plant Breeding. Like our roundtable on Gene-edited Animals in Agriculture (the report from which was sent to you), the attendees represented a broad range of views, including those of major biotechnology plant breeders.

We are in the currently process of producing a report from this meeting and, thus, may not be able to share the final report with you before you complete your own reporting. However, broadly speaking, while a core purpose of plant breeding is continual improvement, all the attendees recognised a variety of limits – both intrinsic and extrinsic – on the process.

Contrary to the assertions of Ms Dupont-Ingliss of EuropaBio in the final session of the day, these limits cannot simplistically be attributed to 'activists 'standing in the way of innovation. For example, limits on any technological innovation can be set by:

- **Differing values and worldviews** – e.g. a systems based approach to problem solving versus a more linear approach.
- **Regulation** – including the difficulty of keeping up with the speed of technological advances
- **Environmental factors** – e.g. climate change, recognition of the need for biodiversity, precaution over invasive species
- **Biological limits** – often these become apparent slowly and over time
- **Ethical factors** – e.g. in somatic versus germline treatments in human genome editing, lack of labelling of food products
- **Economic factors** – including reasonable return on investment
- **Time** – not just for R&D but for risk assessment and proof of benefits
- **Public acceptance** – public distrust narrows markets
- **Power concentration and monopolisation within ind**ustry – keeps ownership of technology in the hands of a relative few
- **The presence of viable non-tech or low-tech alternatives** – if something else works as well or better, why do we need GE?

In the last several decades, many of these factors have played a part in placing limits on biotechnology across multiple applications. While limitations can shift, change and even disappear over time, we can only work with where we are now. Based on what was said during the roundtable, I would suggest that abandoning precaution would be premature and, ultimately, penalise both developers and the public.

Thank you for your attention to these matters.

Yours Sincerely,

Pat Thomas
Director
Beyond GM, UK